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ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: USE OF L-CARNITINE FOR THE TREATMENT OF CARDIOVASCULAR DISEASES

(57) Abstract: The use of L-carnitine or one of its pharmaceutically acceptable salts is described for the preparation of a medicine useful for reducing the number of deaths caused by acute myocardial infarction and for improving the short-and-long-term prognosis in the patients treated with it, in which L-carnitine is administered parenterally within the first few hours of onset of the symptoms of acute myocardial infarction at an initial dose of 9 grams a day for 5 days, after which the treatment is continued at a dose of 4 grams a day by the enteral route.

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**“Use of L-carnitine for the treatment of cardiovascular diseases”**

The invention described herein relates to the use of L-carnitine as a medicine useful for reducing the number of deaths caused by acute myocardial infarction and for improving the short- and long-term prognosis in the patients treated, in which the L-carnitine is administered parenterally within the first few hours of onset of the symptoms of acute myocardial infarction, at an initial dose of 9 grams a day for 5 days, after which the treatment is continued at a dose of 4 grams a day by the enteral route.

Acute myocardial infarction (AMI) causes morphofunctional alterations that often induce progressive left ventricular dilatation (ventricular remodelling” phenomenon).

Post-AMI ventricular dilatation can be regarded as an overall compensation mechanism aimed at maintaining an adequate cardiac output in the presence of a reduction of the ejection fraction.

The extent of the ventricular dilatation is the most important prognostic indicator in patients with AMI.

Patients with relatively larger ventricular volumes are at greater risk of future cardiac events (Circulation 1987; 76:44-51).

Limiting the ventricular remodelling phenomenon in the post-infarction period is thus of great importance from the clinico-prognostic point of view (Circulation 1994; 89:68-75). Limitation of

this phenomenon can be achieved by two mechanisms: (a) by limiting the extent of the infarcted area (which is the main determinant of future dilatation) by means of early myocardial reperfusion (Circulation 1989; 79:441-444) and/or (b) by reducing the parietal stress and consequently the progressive dilatation of the myocardial area not involved in the infarction process by means of the administration of ACE inhibitors.

When the thrombotic obstruction evolves rapidly towards complete, permanent, vascular occlusion, the resulting lack of perfusion gives rise, in the space of a few hours, to myocardial cell necrosis and thus to infarction. The immediate and long-term prognosis will depend upon a series of factors, the most important of which are the size of the necrotic area and the early and late complications resulting from it. It is therefore obvious that the primary aim of modern therapy for acute infarction is to reduce the size of the infarcted area. This objective is achieved with reperfusion procedures, whether pharmacological (thrombolytic agents), mechanical (PTCA), such as angioplasty, or surgical (bypass). Generally, the earlier and more effective the reperfusion, the smaller will be the necrotic area. The latter is also influenced, albeit to a lesser extent, by other factors, and above all by the consumption of myocardial oxygen, which is conditioned by the object's heart rate, myocardial contractility and parietal tension. Of fundamental importance, then, will be all those measures,

whether pharmacological or otherwise, that reduce cardiac work, while at the same time maintaining an adequate circulatory capacity.

More than half of all objects that die of infarction do so during the first few hours.

Useful drugs for the treatment of acute myocardial infarction are already known.

Beta-blockers are drugs endowed with antiarrhythmia properties and are significantly more active if used in the early stages of the onset of the infarction.

Nitroderivatives are drugs administered usually by venous infusion and are useful for enhancing myocardial perfusion through the vasodilatation of the epicardial vessels.

Sodium nitroprussiate is a drug that exerts a double action on the arteriolar and venous districts. This compound produces coronary and renal vasodilatation, thus enhancing myocardial perfusion and diuresis.

L-carnitine is a known compound, the preparation procedure of which is described in US 4,254,053.

The use of L-carnitine for the treatment of cardiac diseases is already well known.

In Drugs Exp Clin Res 1992;18(8):355-65, the authors describe the use of L-carnitine in infarct victims, in which oral treatment with L-carnitine was initiated after the patients had been discharged from hospital. In this report, the authors do not describe or suggest that L-carnitine is useful in preventing death  
5 in the course of acute myocardial infarction.

In Eur Heart J 1989 Jun;10(6):502-8, the authors describe the use of L-carnitine in infarct victims, in which the antiarrhythmia and metabolic effects of L-carnitine are evaluated.  
10 In this study it is reported that there were two deaths each in the group treated with L-carnitine and in that treated with placebo, respectively.

In J Am Coll Cardiol 1995 Aug;26(2):380-7, the authors describe the prolonged use of L-carnitine in infarction patients, and its effect on left ventricular volume at 3, 6 and 12 months  
15 after the start of treatment. In this study L-carnitine was administered within 24 hours of the infarction and the mortality assessment showed that 11 patients in the treated group and 14 in the control group died during the hospitalisation period. The  
20 non-significance of the difference between the number of deaths recorded in the two groups is evident.

In Am Heart J 2000 Feb;139(2 Pt 3):S115-9, which is a review of the metabolic effects of L-carnitine in the cardiological

field, the authors report that L- carnitine is effective because it has metabolic effects on lipid and glucose metabolism.

5 In Lancet 1982 Jun 19;1(8286):1419-20, the authors report that analyses of cardiac tissue samples from patients who died of infarction, in parallel with samples of cardiac tissue from subjects who died of diseases other than infarction, show that, in the cardiac areas not affected by infarction (of the heart disease patients) the levels of free carnitine were the same as those in controls, whereas the free carnitine levels in areas of infarcted  
10 cardiac tissue were lower than in controls.

In Postgrad Med J 1996 Jan;72(843):45-50, the authors describe the use of L-carnitine in patients manifesting infarction symptoms in the 24-hour period prior to the start of treatment. In this study, L-carnitine was administered at a dose of 2 g/day, and  
15 the number of deaths at 28 days after the start of treatment was 6 in the control group and 4 in the treated group. The non-significance of the difference in the number of deaths recorded in the two groups tested is evident.

In Am J Cardiovasc Pathol 1990;3(2):131-42, the authors  
20 describe the use of L-carnitine in an experimental model of cardiac ischaemia in experimental animals (dogs), in which L-carnitine proved to be active in improving cardiac lipid metabolism in these animals.

In this study, the authors do not describe or suggest that L-carnitine is useful in preventing deaths in the course of acute myocardial infarction.

5 There are numerous other publications dealing with the use of L-carnitine in the cardiological field; neither these nor the above-mentioned publications describe or suggest the use of L-carnitine as a medicine useful for reducing the number of deaths caused by acute myocardial infarction, in which L-carnitine is administered intravenously within the first few hours of onset of  
10 acute myocardial infarction symptoms.

The only document of known technique to be found which described the use of L-carnitine within the first few hours of acute myocardial infarction is in Drugs Exptl. Clin. Res. X(4) 219-223 (1984). In this publication, the authors describe the use of L-carnitine at a dose of 40 mg/kg/day (2.8 g/day), and the number  
15 of deaths in the control group was one as against none in the treated group. Moreover, in this study, the treated group was divided into two subgroups, one of which was treated with L-carnitine within 4 hours of the onset of infarct symptoms, while  
20 the other was treated more than 4 hours after the onset of infarct symptoms. In their discussion of the results, the authors state that they found no significant difference between patients treated within 4 hours of the onset of infarct symptoms and those treated more than 4 hours after the onset of such symptoms.

In another publication entitled "Clinical aspects of human carnitine deficiency" published by Pergamon Press in 1986, the authors describe a blind clinical trial in which 351 patients with acute myocardial infarction were recruited, whose  
5 infarct symptoms had started within 8 hours of the start of treatment with L-carnitine. In this clinical trial, the patients received 3 grams of L-carnitine every 8 hours (9 grams a day) by the intravenous route, and the L-carnitine treatment was continued for 48 hours (the control group received saline  
10 solution). The mortality analysis revealed that there was no significant difference between the control group and the L-carnitine-treated group at 7 days after the start of treatment.

This provides further confirmation of the fact that the known technique not only does not demonstrate or suggest the use of L-carnitine in the early stages after onset of an infarction in order to  
15 reduce the number of deaths, but, if anything, prejudices one technically against such use in that L-carnitine has the same effect whether used within the first few hours of an infarction or later.

20 In the medical field it is very important to use drugs at the time most suitable for treating a given disease, such as, for example, acute myocardial infarction. The above-mentioned beta-blockers prove significantly more active if used in the early stages of onset of an infarction.



A given number of patients with acute myocardial infarction continue to die in the first week of hospitalisation and later, even when treated with all appropriate and available pharmacological and technical means. Furthermore,  
5 L-carnitine alone in the therapeutic regimens adopted to date and described in the above-mentioned publications, or in combination with said suitable and available pharmacological and technical means, though improving the treated patient's general condition, fails to reduce the number of deaths as compared to patients  
10 treated with the normal drugs used.

There is therefore a strongly perceived need for the availability of new and known drugs which are useful for reducing the number of deaths due to acute myocardial infarction, where said drugs are used alone or in combination with the normal  
15 known drugs which alone would not be capable of saving from death that proportion of patients who die all the same within the first week or later after the onset of infarction.

It has now been found, surprisingly and unexpectedly, that L-carnitine or one of its pharmaceutically acceptable salts is  
20 capable of reducing the number of deaths caused by acute myocardial infarction, and of improving the prognosis in the short and long term in the patients treated with it, in which said L-carnitine is administered intravenously within the first few hours of onset of AMI symptoms at an initial dose of 9 grams a day for 5

days, after which the treatment is continued at a dose of 4 grams a day by mouth.

What is meant by a pharmaceutically acceptable salt of L-carnitine is any salt of the latter with an acid that does not give  
5 rise to toxic or side effects.

These acids are well known to pharmacologists and to experts in pharmacy. Examples of such salts, though not exclusively these, are: chloride, bromide, orotate, aspartate, acid aspartate, acid citrate, magnesium citrate, phosphate, acid  
10 phosphate, fumarate and acid fumarate, magnesium fumarate, lactate, maleate and acid maleate, oxalate, acid oxalate, pamoate, acid pamoate, sulphate, acid sulphate, glucose phosphate, tartrate and acid tartrate, glycerophosphate, mucate, magnesium tartrate, 2-amino-ethane sulphonate, magnesium 2-amino-ethane  
15 sulphonate, methane sulphonate, choline tartrate, trichloroacetate, and trifluoroacetate.

What is meant by a pharmaceutically acceptable salt of L-carnitine, moreover, is an FDA-approved salt listed in Int. J Pharm. 33 (1986), 201-217, which is incorporated herein for  
20 reference purposes.

One object of the present invention therefore is the use of L-carnitine or one of its pharmaceutically acceptable salts for the preparation of a medicine useful for reducing the number of

deaths caused by acute myocardial infarction and for improving the short- and long-term prognosis in the patients treated, in which L-carnitine is administered intravenously within the first few hours of onset of the symptoms of acute myocardial infarction at an initial dose of 9 grams a day for 5 days, after  
5 which the treatment is continued at a dose of 4 grams a day by mouth.

A further object of the present invention is the use of L-carnitine or one of its pharmaceutically acceptable salts for the preparation of a medicine useful for reducing the number of  
10 deaths caused by acute myocardial infarction and for improving the short- and long-term prognosis in the patients treated, in which L-carnitine is administered intravenously within 6 hours of onset of the symptoms of acute myocardial infarction at an initial  
15 dose of 9 grams a day for 5 days, after which the treatment is continued at a dose of 4 grams a day by mouth.

A further object of the present invention is the use of L-carnitine or one of its pharmaceutically acceptable salts for the preparation of a medicine useful for reducing the number of  
20 deaths caused by acute myocardial infarction and for improving the short- and long-term prognosis in the patients treated, in which L-carnitine is administered intravenously within 4 hours of onset of the symptoms of acute myocardial infarction at an initial

dose of 9 grams a day for 5 days, after which the treatment is continued at a dose of 4 grams a day by mouth.

A further object of the present invention is the use of L-carnitine or one of its pharmaceutically acceptable salts in combination with one or more known drugs, and/or known mechanical and/or surgical techniques, which alone would fail to reduce the number of deaths in infarct victims, for the preparation of a medicine useful for reducing the number of deaths caused by acute myocardial infarction and for improving the short- and long-term prognosis in the patients treated with it, in which L-carnitine is administered intravenously within the first few hours of onset of the symptoms of acute myocardial infarction at an initial dose of 9 grams a day for 5 days, after which the treatment is continued at a dose of 4 grams a day by mouth.

A further object of the present invention is the use of L-carnitine or one of its pharmaceutically acceptable salts in combination with one or more known drugs, and/or known mechanical and/or surgical techniques, which alone would fail to reduce the number of deaths in infarct victims, for the preparation of a medicine useful for reducing the number of deaths caused by acute myocardial infarction and for improving the short- and long-term prognosis in the patients treated, in which L-carnitine is administered intravenously within 6 hours of onset of the symptoms of acute myocardial infarction at an initial dose of 9

grams a day for 5 days, after which the treatment is continued at a dose of 4 grams a day by mouth.

A further object of the present invention is the use of L-carnitine or one of its pharmaceutically acceptable salts in combination with one or more known drugs, and/or known mechanical and/or surgical techniques, which alone would fail to reduce the number of deaths in infarct victims, for the preparation of a medicine useful for reducing the number of deaths caused by acute myocardial infarction and for improving the short- and long-term prognosis in the patients treated, in which L-carnitine is administered intravenously within 4 hours of onset of the symptoms of acute myocardial infarction at an initial dose of 9 grams a day for 5 days, after which the treatment is continued at a dose of 4 grams a day by mouth.

Examples of said known drugs used in intensive care which alone would fail to reduce the number of deaths in infarct victims are, though not exclusively, the following: beta-blockers, calcium antagonists, aspirin, angiotensin converting enzyme inhibitors, or ACE inhibitors, in which said ACE inhibitor is selected from the group consisting of alacepril, benazepril, benazeprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enaprilat, fosinopril, imidapril, indolapril, lisinopril, moveltipril, perindopril, pentopril, pivalopril, quinapril, ramipril, spirapril, temocapril, trandolapril or zofenopril.

The preferred calcium antagonists are diltiazem, nifedipine, verapamil, nicardipine and nimodipine.

The preferred mechanical and/or surgical techniques are angioplasty and by-pass.

5 The following example illustrates the invention.

**Example 1**

10 A clinical trial was conducted in order to evaluate the effect of the administration of L-carnitine on the incidence of mortality and heart failure in the short and long term in patients with acute myocardial infarction. The trial design was that of a multicentre, parallel-group, double-blind, placebo-controlled, randomised trial.

15 A total of 2,296 male and female patients aged below 80 years were recruited. The study compound, L-carnitine, was administered at a dose of 9 g/day i.v. for the first 5 days and 4 g/day by mouth from day 6 to day 180.

Concomitant therapies were given according to the procedures adopted in local clinical practice.

The efficacy endpoints of the trial consisted in the reduction of mortality and heart failure.

20 **Inclusion criteria**

- Typical chest pain lasting > 30 minutes, not resolved by the oral or intravenous administration of nitrates;
- ECG with ST segment deviation  $\geq 0.2$  mV in D, and aVL and/or in two or more contiguous precordial leads;

- Time interval elapsing from onset of symptoms to trial randomisation < 12 hours;
- Age < 80 years;
- Written informed consent.

#### 5 **Exclusion criteria**

- Pregnancy or breast-feeding;
- Haemodynamically significant valvulopathy;
- Hypertrophic or dilated cardiomyopathy;
- Congenital heart disease;
- 10 - Clinically severe liver or kidney disease;
- Alcohol abuse;
- Other diseases associated with a poor life expectancy;
- Conditions making poor compliance with treatment and/or periodic visits likely;
- 15 - Inclusion in another trial.

The results obtained are presented in Table 1.

**Table 1**

	NUMBER OF DEATHS AT:						
	3 days	5 days	7 days	1 mos	2 mos	6 mos	12 mos
Placebo	34	43	45	58	65	74	75
L-carnitine	23	27	31	45	53	64	67
RR	0.68	0.63	0.69	0.78	0.81	0.86	0.89
P	0.1357	0.0498	0.097	0.1766	0.238	0.3546	0.4555

RR = Relative Risk

20 These results show that the compound according to the invention, with the particular treatment regimen adopted in this

clinical trial, induced a statistically significant reduction in deaths after 5 days' treatment ( $P<0.05$ ) and significant reductions at the other observation times.

5 The L-carnitine doses used according to the present invention and the treatment regimen may be varied at the discretion of the primary care physician on the basis of his or her experience and the patient's general condition, also thanks to the lack of toxicity of the compound according to the invention.

10 The formulations for intravenous administration, according to the present invention, consist of solutions or suspensions in suitable vehicles such as saline solution, distilled water, glucose solution, or others.

15 The formulations for oral administration, according to the present invention, consist of tablets, capsules, powders, granules, syrups, elixirs, solutions or suspensions.

The compound according to the invention can be administered in single or multiple doses.

20 When the compound according to the invention (in single or multiple doses) is administered in combination with one or more of the above-mentioned known drugs used in the intensive care which alone would fail to reduce the number of deaths in infarct victims, said combination can be administered as a single pharmaceutical composition combining the active ingredients in a pharmaceutically acceptable vehicle, or said active ingredients can be administered



separately, simultaneously, or in sequence, via the same or different administration routes

When the compound according to the present invention is administered in combination with other drugs, the administration  
5 can be effected in any suitable dosage form combination, e.g. in the form of oral L-carnitine/oral drug used in combination with it; or injectable L-carnitine/oral drug used in combination with it; or oral L-carnitine /injectable drug used in combination with it.

10 The present invention also relates to a kit combining the active ingredients, separately, in a single pack.

This kit is particularly useful when the components have to be administered by different routes and/or at different times.

**CLAIMS**

1. The use of L-carnitine or one of its pharmaceutically acceptable salts for the preparation of a medicine useful for reducing the number of deaths caused by acute myocardial infarction and  
5 for improving the short- and long-term prognosis in the patients treated with it, in which L-carnitine is administered intravenously within the first few hours of onset of the symptoms of acute myocardial infarction at an initial dose of 9 grams a day for 5 days, after which the treatment is continued  
10 as a dose of 4 grams a day by mouth.
2. Use of L-carnitine or one of its pharmaceutically acceptable salts in combination with one or more known drugs, and/or known mechanical and/or surgical techniques, which alone would fail to reduce the number of deaths in infarct victims, for  
15 the preparation of a medicine useful for reducing the number of deaths caused by acute myocardial infarction and for improving the short and long-term prognosis in the patients treated, in which L-carnitine is administered intravenously within the first few hours of onset of the symptoms of acute myocardial  
20 infarction at an initial dose of 9 grams a day for 5 days, after which the treatment is continued at a dose of 4 grams a day by mouth.

3. Use according to claim 1 or 2, in which L-carnitine is administered intravenously within 6 hours of onset of the symptoms of acute myocardial infarction.
4. Use according to claim 1 or 2, in which L-carnitine is administered intravenously within 4 hours of onset of the symptoms of acute myocardial infarction.
5. Use according to claims 1-4 in which the pharmaceutically acceptable salt of L-carnitine is selected from the group consisting of chloride, bromide, orotate, aspartate, acid aspartate, acid citrate, magnesium citrate, phosphate, acid phosphate, fumarate and acid fumarate, magnesium fumarate, lactate, maleate and acid maleate, oxalate, acid oxalate, pamoate, acid pamoate, sulphate, acid sulphate, glucose phosphate, tartrate and acid tartrate, glycerophosphate, mucate, magnesium tartrate, 2-amino-ethane sulphonate, magnesium 2-amino-ethane sulphonate, methane sulphonate, choline tartrate, trichloroacetate, and trifluoroacetate.
6. Use according to claim 2, in which the drug which alone would fail to reduce the number of deaths in infarct victims is selected from the group consisting of beta-blockers, calcium antagonists, aspirin, angiotensin converting enzyme inhibitors, or ACE inhibitors.

7. Use according to claim 6, in which the ACE inhibitor is selected from the group consisting of: alacepril, benazepril, benazeprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enaprilat, fosinopril, imidapril, indolapril, lisinopril, 5 moveltipril, perindopril, pentopril, pivalopril, quinapril, ramipril, spirapril, temocapril, trandolapril or zofenopril.
8. Use according to claim 6, in which the calcium antagonist is selected from the group consisting of diltiazem, nifedipine, verapamil, nicardipine or nimodipine.
- 10 9. Use according to claim 2, in which the mechanical technique is angioplasty and the surgical technique by-pass.
10. Use according to claim 1 or 2, in which the L-carnitine for oral administration is in the form of tablets, capsules, powders, granules, syrups, elixirs, suspensions or solutions.
- 15 11. Use according to claim 1 or 2, in which the L-carnitine for intravenous administration is in the form of suspensions or solutions in suitable vehicles.
12. Use according to claim 11, in which the vehicle is selected from the group consisting of distilled water, saline solution or glucose 20 solution.
13. Use according to claim 2, in which the combination can be administered in a single pharmaceutical composition combining the active ingredients in a suitable pharmaceutically acceptable vehicle.

14. Use according to claim 2, in which the active ingredients can be administered separately in parallel or in sequence.
15. Use according to claim 2, in which the active ingredients present in the combination can be administered in any  
5 suitable dosage form or combinations thereof.
16. Use according to claim 2, in which the combination is in the form of a kit combining the active ingredients, separately, in a single pack.
17. Use according to claim 16, in which the kit components are  
10 administered by different routes and/or at different times.

# INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER  
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According to International Patent Classification (IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ILICETO SABINO ET AL: "Effects of L-carnitine administration on left ventricular remodeling after acute anterior myocardial infarction: The L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) trial" JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 26, no. 2, 1995, pages 380-387, XP002290008 ISSN: 0735-1097 page 382, right-hand column, last paragraph page 381, left-hand column, Methods table 2 ----- -/--	1-6, 10-12, 15

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IT2004/000107

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	COLONNA PAOLO ET AL: "Myocardial infarction and left ventricular remodeling: Results of the CEDIM trial" AMERICAN HEART JOURNAL, vol. 139, no. 2 Part 3, February 2000 (2000-02), pages S124-S130, XP008033144 ISSN: 0002-8703 page S127, left-hand column page S129, left-hand column, paragraph 4 -----	1-5, 10-12,15
X	MARTINA B ET AL: "Antiarrhythmic treatment with L-carnitine in acute myocardial infarction" SCHWEIZERISCHE MEDIZINISCHE WOCHENSCHRIFT, vol. 122, no. 37, 1992, pages 1352-1355, XP008033145 ISSN: 0036-7672 page 1353, left-hand column, "Patienten und Methoden" page 1354, right-hand column, "Diskussion" -----	1-5, 10-12,15
X	RIZZON P ET AL: "HIGH DOSES OF L CARNITINE IN ACUTE MYOCARDIAL INFARCTION METABOLIC AND ANTIARRHYTHMIC EFFECTS" EUROPEAN HEART JOURNAL, vol. 10, no. 6, 1989, pages 502-508, XP008033143 ISSN: 0195-668X page 503, left-hand column, "Materials and Methods" page 507, left-hand column, last paragraph table 6 -----	1-6, 10-12,15
X	SINGH R B ET AL: "A randomised, double-blind, placebo-controlled trial of L-carnitine in suspected acute myocardial infarction" POSTGRADUATE MEDICAL JOURNAL, vol. 72, no. 843, 1996, pages 45-50, XP008033142 ISSN: 0032-5473 page 45, right-hand column, last paragraph page 46, left-hand column, "Treatments" page 46, left-hand column, "Study design" page 47, right-hand column, "Discussion" page 48, right-hand column, paragraph 1 -----	1-6, 10-12,15